

University of Groningen

Synthesis of Carbapenems with a RXCH₂-Substituent in the 3-Position

Vries, Johannes G. de; Sigmund, Gerhard; Vorisek, Georg

Published in:
 HETEROCYCLES

DOI:
[10.3987/R-1985-08-1915](https://doi.org/10.3987/R-1985-08-1915)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
 Publisher's PDF, also known as Version of record

Publication date:
 1985

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Vries, J. G. D., Sigmund, G., & Vorisek, G. (1985). Synthesis of Carbapenems with a RXCH₂-Substituent in the 3-Position. *HETEROCYCLES*, 23(8). <https://doi.org/10.3987/R-1985-08-1915>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

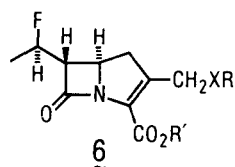
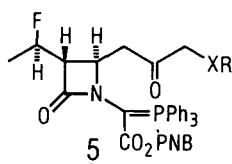
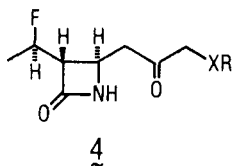
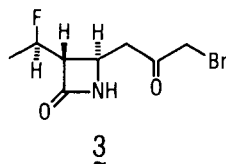
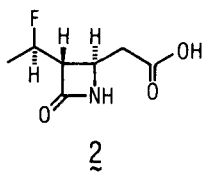
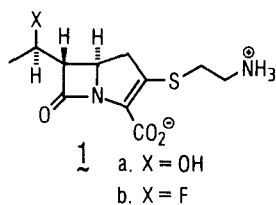
SYNTHESIS OF CARBAPENEMS WITH A $RXCH_2$ -SUBSTITUENT IN THE 3-POSITIONJohannes G. de Vries*¹, Gerhard Sigmund, and Georg Vorisek

Sandoz Forschungsinstitut, Brunnerstraße 59, A-1235 Vienna, Austria

Abstract - Carbapenems **6** were prepared by reacting mercaptans with bromoketone **3** followed by a Wittig sequence, or better through advanced intermediate **9**. The carbapenem carboxylates were chemically unstable; stability was not improved by changing the oxidation state of sulfur.

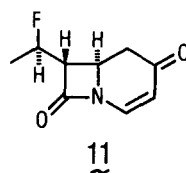
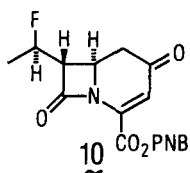
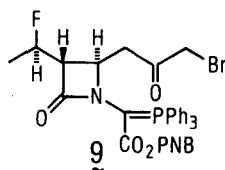
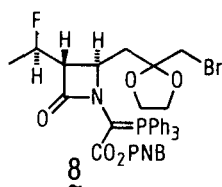
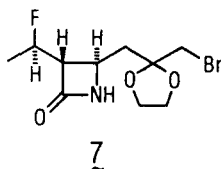
Ever since the discovery of thienamycin (**1a**) a large number of analogues have been synthesized in an attempt to improve the chemical and metabolic instability of thienamycin while retaining its potent antibacterial activity². Our efforts in this area have been concentrated on carbapenems with an R -1-fluoroethyl side chain in the 6-position³. In this paper we report our synthetic work on carbapenems bearing a CH_2XR side chain in the 3-position⁴: we hoped that insertion of a methylene group in between nucleus and sulfur side chain would provide additional chemical and metabolic stability. From the viewpoint of synthetic efficiency introduction of the variable RX group should occur as late as possible in the synthetic sequence. We therefore chose 3-acetoxymethylcarbapenem ester **6a** as intermediate, based upon the knowledge that 3-acetoxymethylcephalosporins react with mercaptans to give the thio substituted analogues⁵.

Starting with acid **2**^{3a,b} we were able to synthesize the bromoketone **3**⁶ (41%⁷, mp 71-73°C) by a Nierenstein sequence⁸ (see Reaction Conditions). Reaction with NaOAc in DMF gave the acetoxy compound **4a** in 88% yield which was transformed into the desired 3-acetoxymethylcarbapenem **6a** by the Wittig procedure developed by Woodward⁹ (44% over 4 steps). Unfortunately, reaction of **6a** with lithium benzyl sulfide (THF, -30°C) led to unidentifiable products and reaction with $PhCH_2SH/Et_3N$ (CH_2Cl_2 , RT) gave only recovered **6a**. Addition of $Pd(Ph_3P)_4$ to the latter reaction had no beneficial effect. Before investigating other strategies we decided to synthesize one representative of **6** by an alternative route. Reaction of **3** with $PNBO_2CNHCH_2CH_2SH$ ¹⁰ gave **4b** (76%), which was converted to **6b** in the usual way (20%, yield over 4 steps). Hydrogenation of **6b** gave **6c** in 19% yield (purity 80% by ¹H NMR)



- 4,5: a. RX = OAc
b. RX = SCH₂CH₂NHCO₂PNB
c. RX = SCH₂-3-Pyr.

- 6: a. RX = OAc R' = PNB
b. RX = SCH₂CH₂NHCO₂PNB R' = PNB
c. RX = SCH₂CH₂NH₂ R' = H
d. RX = SCH₂-3-Pyr R' = PNB
e. RX = SCH₂-3-Pyr R' = H
f. RX = SOCH₂CH₂NHCO₂PNB R' = PNB
g. RX = SOCH₂CH₂NH₂ R' = H
h. RX = SOCH₂-3-Pyr R' = PNB
i. RX = SOCH₂-3-Pyr R' = H
j. RX = SO₂CH₂CH₂NHCO₂PNB R' = PNB
k. RX = H R' = H
l. RX = SO₂CH₂-3-Pyr R' = PNB
m. RX = SO₂CH₂-3-Pyr R' = H



REACTION CONDITIONS

$\underline{2} \rightarrow \underline{3}$:	i. $(\text{CH}_3)_2\text{CHCH}_2\text{O}_2\text{CCl}$, Et_3N , CH_2Cl_2 , -78°C . ii CH_2N_2 , $-30^\circ \rightarrow -10^\circ\text{C}$. iii. HBr , -40°C .
$\underline{3} \rightarrow \underline{4a}$:	NaOAc , DMF , RT .
$\underline{3} \rightarrow \underline{4b}$:	$\text{PNBO}_2\text{CNHCH}_2\text{CH}_2\text{SH}$, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , 0°C .
$\underline{3} \rightarrow \underline{4c}$:	$3\text{-PyrCH}_2\text{SH}$, Et_3N , CH_2Cl_2 , 0°C .
$\underline{4} \rightarrow \underline{5}$:	i $\text{PNBO}_2\text{CCH}(\text{OH})_2$, benzene, azeotropic reflux. ii SOCl_2 ,
$\underline{7} \rightarrow \underline{8}$	Et_3N , THF , -20°C . iii Ph_3P , THF , RT .
$\underline{5} \rightarrow \underline{6}$:	Toluene, 1% hydroquinone, reflux.
$\underline{6b}, \underline{d} \rightarrow \underline{6f}, \underline{h}$:	1 eq. MCPBA, CH_2Cl_2 , -30°C .
$\underline{6b}, \underline{d} \rightarrow \underline{6j}, \underline{l}$:	2 eq. MCPBA, CH_2Cl_2 , 0°C .
$\underline{6b}, \underline{d}, \underline{f}, \underline{h}, \underline{j}, \underline{l} \rightarrow$:	Pd/C 10% (eq. amount w/w to $\underline{6}$), H_2 , THF , Phosphate
$\underline{6c}, \underline{e}, \underline{g}, \underline{i}, \underline{k}, \underline{m}$	buffer pH 7.
$\underline{3} \rightarrow \underline{7}$:	$(\text{CH}_2\text{OH})_2$, PPTS, benzene, azeotropic reflux.
$\underline{8} \rightarrow \underline{9}$:	70% aq. HClO_4 , CH_2Cl_2 , 8 min.
$\underline{9} \rightarrow \underline{10} + \underline{11}$:	CH_3CN , RT , 16 hrs.

after RP-18 column chromatography and lyophilization. Though $\underline{6c}$ was very unstable¹¹, we were able to establish that the compound had a satisfactory antibacterial spectrum and had improved renal dehydrogenase stability compared to the fluorinated thienamycin $\underline{1b}$ ^{3b}. Encouraged by this finding we set out to synthesize more analogues, soon to find out that the sequence $\underline{4} \rightarrow \underline{5}$ is of limited value because of the incompatibility of many functional groups with SOCl_2 . So, clearly the synthetic sequence had to be adapted in such a way as to allow introduction of the variable side chain at a later stage. Thus we protected bromoketone $\underline{3}$ as the ketal $\underline{7}$ (77 %) which was transformed into phosphorane $\underline{8}$ (74 %). The ketal function in $\underline{8}$ was very stable and deprotection turned out to be a serious problem. After many unsuccessful attempts we found that $\underline{8}$ could be hydrolyzed in CH_2Cl_2 solution by brief treatment with a large excess of 70% aqueous HClO_4 (99%)¹². The resulting bromoketone was very unstable and was best immediately reacted with mercaptan and base. A solution of $\underline{9}$ in CH_3CN left overnight gave $\underline{10}$ and $\underline{11}$ as main products. Reaction of $\underline{9}$ with 3-pyridylmethyl mercaptan and Et_3N gave $\underline{5c}$ (100%) which was cyclized to $\underline{6d}$ (64%), which we had not been able to obtain by the original sequence: $\underline{4c}$ had perished in the second step of the Woodward sequence. Catalytic hydrogenation of $\underline{6d}$ did produce the expected carbapenem potassium salt $\underline{6e}$ (3%), but this compound was so unstable that no biological data could be obtained. We then sought to find out if the stability of these compounds is influenced by the oxidation state of the sulfur in the side chain. Oxidation of $\underline{6b}$ and $\underline{6d}$ with 1 eq. of MCPBA gave the sulfoxides $\underline{6f}$ (51%) and $\underline{6h}$ (61%); with 2 eq. MCPBA the sulfones $\underline{6j}$ (41%) and $\underline{6l}$ (47%) were obtained. Deprotection of the

sulfoxides 6f and 6h and the sulfone 6l proceeded as usual to give 6g (15%), 6i (46%) and 6m (47%), respectively; but the stability of these compounds was very similar to those of the parent sulfides. Deprotection of 6j was accompanied by reduction of the allylic sulfone, giving 3-methylcarbapenem carboxylate 6k¹³.

Since it is possible that the instability of these carbapenems is due to the presence of a potential leaving group on methyl we have now shifted our attention to aminoalkyl substituted carbapenems and we will report on this in due course.

ACKNOWLEDGEMENTS

Thanks are due to Dr. G. Schulz for interpretation of NMR spectra and to Drs. F. Turnowsky and J. Hildebrandt for biological testing.

REFERENCES

1. Present address: Sandoz Institute for Medical Research, c/o University College, Gower Street, London, WC1E 6BT.
2. R.W. Ratcliffe and G. Albers-Schönberg in "Chemistry and Biology of β -Lactam Antibiotics", Vol. 2, p 227, edited by R.B. Morin and M. Gorman, Academic Press, 1982.
3. (a) C.P. Mak, K. Wagner, C. Mayerl, and H. Fliri, Heterocycles, 1982, **19**, 1399.
(b) C.P. Mak and H. Fliri, Belgian Patent 897351-A, 1982.
(c) J.G. de Vries, G. Hauser, and G. Sigmund, Tetrahedron Lett., 1984, 5989.
4. Other publications on $RXCH_2$ substituted carbapenems:
(a) E. Götschi, German Patent 3201957 A1, 1982.
(b) T. Hiraoka, T. Kobayashi, N. Ishida, and S. Sugawara, German Patent 3107854 A1, 1982.
(c) M. Shiozaki, N. Ishida, H. Maruyama, T. Hiraoka, and S. Sugawara, J. Antibiotics, 1984, **37**, 57.
5. C.F. Murphy and J.A. Webber in "Cephalosporins and Penicillins, Chemistry and Biology", edited by E.H. Flynn, Academic Press, New York, 1972, p. 134.
6. Selected spectral data (NMR in $CDCl_3$ or D_2O , UV, in H_2O): 3j: 1H NMR: 6.28 (1H, br s, NH), 4.96 (1H, ddq, $J = 48.6, 7.5, 6.3$ Hz, HCF), 4.00 (1H, ddd, $J = 9.5, 3.5, 2.5$ Hz, H-4), 3.91 (s, 2H, CH_2Br), 3.25 and 2.96 (2H, ABX, $J_{AB} = 18.5$ Hz, $J = 7.5, 3.5$ Hz, CH_2CO), 3.02 (1H, ddd, $J = 18.0, 7.5, 2.5$ Hz, H-3), 1.47 (3H, dd, $J = 24.5, 6.3$ Hz, CH_3). 4a: 1H NMR: 4.66 (2H, s, CH_2O), 2.17 (3H, s, Ac). 4b: 1H NMR: 5.24 (2H, s, OCH_2), 3.29 (2H, s, CH_2S). 4c: 1H NMR: 3.70 (2H, s, CH_2Py), 3.12 (2H, s, CH_2S). 6a: 1H NMR: 5.29 and 5.05 (2H, AB, $J = 15.5$ Hz, CH_2OAc), 2.10 (3H, s, Ac), IR (KBr): 1783, 1744, 1710 cm^{-1} . 6b: 1H NMR: 3.80 and 3.66 (2H, AB, $J = 13.5$ Hz, CH_2S). IR (CH_2Cl_2): 1783, 1724 cm^{-1} . 6c: IR (KBr): 1761 cm^{-1} , UV: $\lambda_{max} = 272$ ($\epsilon = 5900$) nm. 6d: 1H NMR: 3.70 (2H, s, CH_2Py), 3.82 and 3.69 (2H, AB, $J = 14.0$ Hz, CH_2S), IR (CH_2Cl_2): 1781, 1721 cm^{-1} . 6e: 1H NMR: 3.32 (1H, ddd, $J = 27.4, 5.1, 2.9$ Hz, H-6), 1.36 (3H, dd, $J = 25.0, 6.3$ Hz, CH_3). 6f: IR (CH_2Cl_2): 1789, 1716, 1700,

1048 cm^{-1} . **6g**: ^1H NMR: 4.32 and 4.19 (2H, AB, $J = 13.5$ Hz, CH_2SO). **6h**: IR (CH_2Cl_2): 1786, 1718, 1055 cm^{-1} . **6i**: IR (KBr): 1762, 1595, 1387, 1029 cm^{-1} . UV: $\lambda_{\text{max}} = 263$ (6.400), 269 (5900) nm. **6j**: ^1H NMR: 4.59 and 4.27 (2H, AB, $J_{\text{AB}} = 14.0$ Hz, CH_2SO_2). IR (CH_2Cl_2): 1789, 1726, 1320, 1114 cm^{-1} . **6k**: ^1H NMR: 2.01 (3H, s, $=\text{C}-\text{CH}_3$). **6l**: ^1H NMR: 4.60 and 4.32 (2H, AB, $J_{\text{AB}} = 14.2$ Hz, CH_2SO_2), 4.30 (2H, s, CH_2Py). IR (CH_2Cl_2): 1787, 1719, 1331, 1120 cm^{-1} . **6m**: ^1H NMR: 4.22 (1H, ddd, $J = 9.5, 9.0, 3.0$ Hz, H-5), 3.61 (1H, ddd, $J = 28.1, 4.5, 3.0$ Hz, H-6). **7**: ^1H NMR: 4.06 (4H, m, CH_2CH_2), 3.36 (2H, s, CH_2Br), 2.42 and 2.13 (2H, ABX, $J_{\text{AB}} = 14.6$ Hz, $J = 9.7, 3.2$ Hz, CH_2). **10**: ^1H NMR: 6.25 (1H, s, $=\text{CH}$), 2.95 and 2.66 (2H, ABX, $J_{\text{AB}} = 16.2$ Hz, $J = 5.4$ and 13.7 Hz, H-5). **11**: ^1H NMR: 7.44 (1H, d, $J = 7.6$ Hz, H-2), 5.54 (1H, d, $J = 7.6$ Hz, H-3), 2.67 and 2.84 (2H, ABX, $J_{\text{AB}} = 16.0$ Hz, $J = 13.0, 6.2$ Hz, H-5). IR (CH_2Cl_2): 1775, 1672, 1585, 1380 cm^{-1} . MS (calcd. for $\text{C}_9\text{H}_{10}\text{FNO}_3$: 183): m/e 183 (M, 18), 136 (M- CH_3CHF , 16), 96 (100).

7. The only side product we have been able to isolate was the isobutyl ester of **2**, but use of other activated derivatives such as the acid chloride or imidazolide did not lead to improved yields of **3**.
8. The synthesis of 3-[2-(*tert*-butyldimethylsilyloxy)-ethyl]-4-(3-chloro-2-oxo-propyl)-2-azetidinone using the Nierenstein reaction has been described: M. Shiozaki, N. Ishida, T. Hiraoka, and H. Maruyama, *Tetrahedron*, 1984, **40**, 1795.
9. R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R.B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 408.
10. W. F. Shukis, A.J. Zambito, and E.J.J. Grabowski, *Synth. Commun.*, 1984, **14**, 613.
11. We were unsuccessful in our attempts to convert **6c** to the *N*-acetimidoyl or *N*-formimidoyl derivatives, a strategy which was successfully applied by Merck chemists to stabilize thi-enamycin: W.J. Leanza, K.J. Wildonger, T.W. Miller, and B.G. Christensen, *J. Med. Chem.* 1979, **22**, 1435.
12. We were not able to hydrolyze **8** using milder methods.
13. A similar allylic reduction was observed by Sankyo chemists: Ref. 4c.

Received, 15th April, 1985